Total Synthesis of Natural PI-091, a New Platelet Aggregation Inhibitor of Microbial Origin

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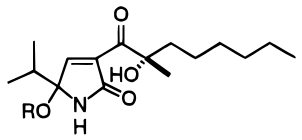
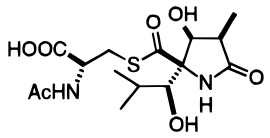
The total synthesis of a new platelet aggregation-inhibiting γ-lactam PI-091 (**1**) gave a 1:1 diastereomeric mixture at the γ-ketal carbon. The high-yielding aldol reaction of an appropriately protected 1,3,4-trihydroxy-4-methyldecan-2-one **42**, prepared from D-glucose, with the kinetically generated enolate of 3-methyl-2-butanone provided **43**. The resulting diastereomeric mixture of the aldol adduct **43** was converted to a 2,4-alkylated furan **45** via an intramolecular ketalization followed by dehydration. The addition of a singlet oxygen to the α-trimethylsilylated furan **48** derived from **45** under photochemical conditions efficiently provided an α,γ-dialkylated γ-hydroxy γ-lactone **47.** The transformation of methyl ketal **52** prepared from **47** into γ-hydroxy γ-lactam **53** was achieved by exposure to liquid ammonia in MeOH. The total synthesis of **1** was achieved from **52** through the Dess−Martin periodinane oxidation of the secondary hydroxy group in the side chain. The present total synthesis revealed that the stereogenic carbon center in the side chain in natural **1** is *S*.

During their screening of new platelet aggregation inhibitors from natural sources, the research group at Taisho Pharmaceutical Co. isolated PI-091 (**1**) from *Paecilomyces* sp. F-3430[1] (Figure 1). Compound **1** exhibits modest arachidonic acid-induced platelet aggregation-inhibitory activity in rabbit with an IC_{50} of 12×10^{-5} M.[1] Compound **1** may be an artifact formed by the methyl ketalization of another natural product designated PI-090 (**2**), which is the hemiketal form of **1**, during purification of extracts from the microorganism on silica gel using methanol as a solvent.[2] The relative stereochemistry of **1** was determined based on spectroscopic analysis (^{1}H NMR, MS, UV, and IR). A structural characteristic of **1** is a γ,γ-*C*,*O*-disubstituted α,β-unsaturated γ-lactam skeleton, which possesses a 2-hydroxy-2-methyloctanoyl group as a side chain at the α-position. Furthermore, **1** exists as an approximately 1:1 diastereomeric mixture at the γ-ketal carbon. Interestingly, this diastereomeric mixture itself exhibits platelet aggregation-inhibitory activity. Recently, two natural products characterized by their highly substituted γ-lactam structure, i.e., lactacystin (**3**)[3] and epolactaene (**4**),[4] were isolated as potent neuritogenic agents. We describe here our total synthesis of **1** in its natural enantiomeric form and show that the absolute configuration of the stereogenic center (C7) in the side chain of **1** is *S* , as depicted in Figure 1.[5]



1 R = Me
2 R = H



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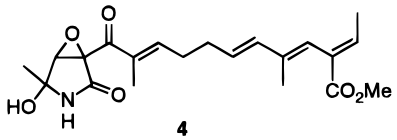

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Figure 1.

At the outset of our efforts, we had no decisive information regarding the stereochemistry at C7 in **1**. We assumed it to be *S* based on the accessibility of an enantiomerically pure starting material for total synthesis. Our retrosynthetic analysis for the enantiomeric total synthesis of **1** is depicted in Scheme 1. The target **1** was expected to be obtained, in a later stage of the total synthesis, from a properly functionalized γ-lactone **A** (P indicates suitable protecting groups) by lactone−lactam transformation, methyl ketalization, and oxidation of the secondary hydroxyl group in the side chain. The target **1** would become a 1:1 diastereomeric mixture at the stage of γ-lactam formation or methyl ketalization. The γ-lactone **A** was to be obtained by the addition of a singlet oxygen to a 2,4-disubstituted furan **B**. The furan **B** was to be prepared from a 1,3,4-trihydroxypentan-2-one derivative **C** by the following reactions: (1) aldol-like

[⊗] Abstract published in *Advance ACS Abstracts,* March 15, 1996.

(1) Kawashima, A.; Yoshimura, Y.; Sakai, N.; Kamigoori, K.; Mizutani, T.; Omura, S. Jpn. Kokai Tokkyo Koho JP 02 62,859[90 62,859] (C1.C07D207/38), 02 Mar 1990, Appl. 88/215,393,30 Aug 1988 (*Chem. Abstr.* **1990**, *113,* 113856d). Manuscript in preparation.

(2) Personal communication from Dr. A. Kawashima (Taisho Pharmaceutical Co., Ltd.)

(3) Isolation: Omura, S.; Fujimoto, T.; Otogura, K.; Matuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44,* 113. Structure determination: Omura, S.; Matsuzaki, T.; Fujimoto, K.; Kosuge, T.; Furuya, T.; Fujita, S.; Nakagawa, A. *Ibid.* **1991**, *44,* 117. Total synthesis: (a) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114,* 10677. Corey, E. J.; Reichard, G. A.; Kania, R. *Tetrahedron Lett.* **1993**, *34,* 6977. (b) Sunazuka, T.; Nagamitsu, T.; Matsuzaki, H.; Tanaka, S.; Omura, S.; Smith, A. B., III. *J. Am. Chem. Soc.* **1993**, *115,* 5302. (c) Uno, H.; Baldwin, J. E.; Russell, A. T. *J. Am. Chem. Soc.* **1994**, *116,* 2139. (d) Chida, N.; Takeoka, J.; Tsutsumi, N.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1995**, 763.

(4) Kakeya, H.; Takahashi, I.; Okada, G.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48,* 733.

(5) Total synthesis of **1** was reported in a preliminary communication form: Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *Tetrahedron Lett.* **1995**, *36* , 5551.

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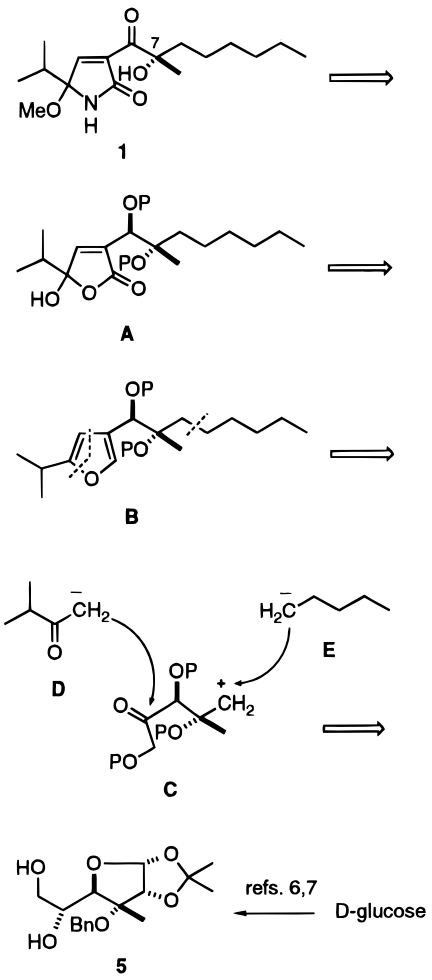
Scheme 1

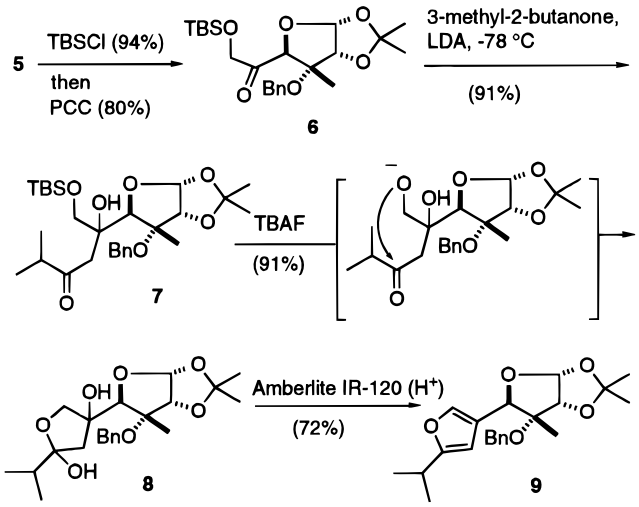


carbon−carbon bond formation between **C** and the kinetically deprotonated anion **D** derived from 3-methyl-2-butanone, and (2) five-carbon elongation with a pentyl anion equivalent **E** through a procedure such as a Wittig olefination. The key intermediate **C** could be considered a synthetic equivalent of a 2-*C*-methyl-4-keto aldopentose. Consequently, as an enantiomerically pure starting material, we selected the stereochemically defined 3-*C*-methylated D-allofuranose **5**, which was readily prepared from D-glucose (Scheme 1).[6,7]

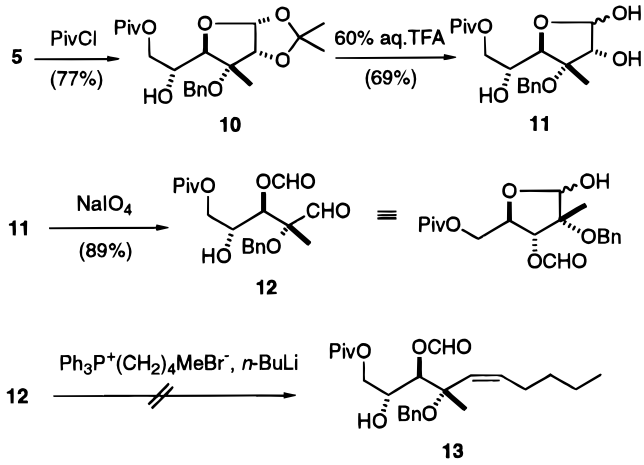
Results and Discussion

In an early stage of our synthetic studies, to obtain synthetic intermediates bearing a 2,4-disubstituted furan (**B** in the retrosynthesis), we explored the modification of the side chain (C5−C6) in **5** to a furan nucleus. The primary hydroxy group in **5** was protected as a *tert*-butyldimethylsilyl (TBS) ether, and the secondary hydroxy group was oxidized with PCC to give 5-ulose **6** (Scheme 2). The aldol reaction of **6** with the kinetic enolate of 3-methyl-2-butanone (generated with LDA at −78 °C) proceeded smoothly to give the aldol adduct **7** in 91% yield. The adduct **7** consists of a single diastereomer, although we could not determine the configuration of the newly introduced stereogenic center unambiguously. As expected, removal of the TBS group in

Scheme 2



Scheme 3

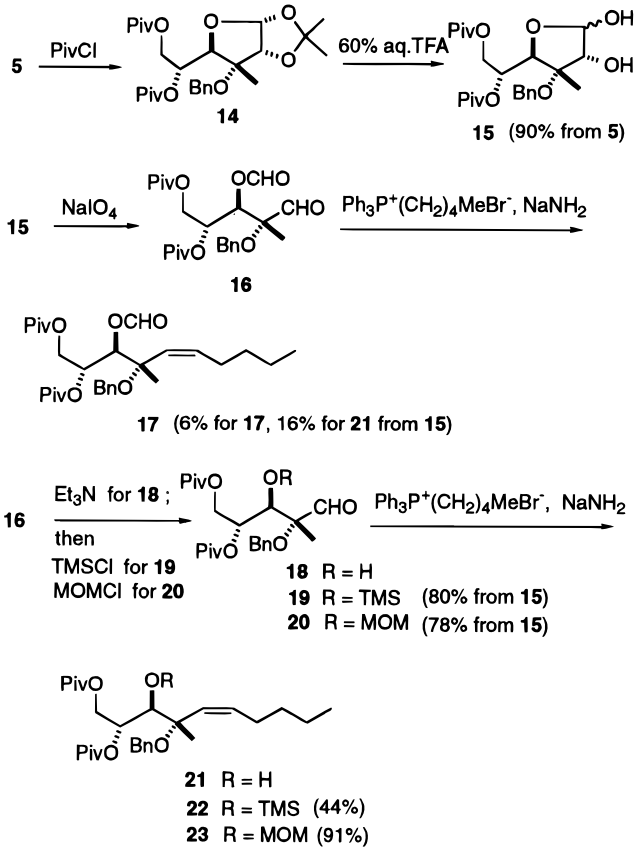


7 with tetra-*n*-butylammonium fluoride (TBAF) resulted in the spontaneous attack of the carbonyl group by the liberated alkoxy anion, leading to tetrahydrofuran diols **8** as an inseparable diastereomeric mixture in 91% yield. The stereochemistry of the newly introduced stereogenic carbons was not determined; however, the diols **8** were immediately dehydrated with IR-120 [H^+] resin in MeOH to give 2,4-disubstituted furan **9**. Unfortunately, we could not find practical reaction conditions for chemoselective hydrolysis of the isopropylidene group in **9**. Under the various acidic conditions examined for this purpose, the formation of complex mixtures predominated and the desired de-*O*-isopropylidene derivative could not be obtained. From these disappointing results, we concluded that it was essential to introduce the five-carbon side chain prior to construction of the furan nucleus.

Preferential esterification of the primary hydroxy group in **5** gave the mono *O*-pivaloyl derivative **10** (Scheme 3). Hydrolysis of the isopropylidene group in **10** with 60% aqueous CF_3COOH (TFA) gave triol **11**. Oxidative cleavage of the glycol in **11** with $NaIO_4$ gave **12**, which exists exclusively in a cyclic hemiacetal form (^1H NMR analysis). Several attempts at the Wittig reaction of hemiacetal **12** to give the five-carbon elongated olefin **13** with the ylide, prepared by base treatment of pentyltriphenylphosphonium bromide, met with difficulty. The hemiacetal **12** was considered to not exhibit an aldehydic character.

(6) Brimacombe, J. S.; Rollins, A. J.; Thompson, S. W. *Carbohydr. Res.* **1973**, *31*, 108.
(7) Funabashi, M.; Yamazaki, S.; Yoshimura, J. *Carbohydr. Res.* **1975**, *44*, 275.

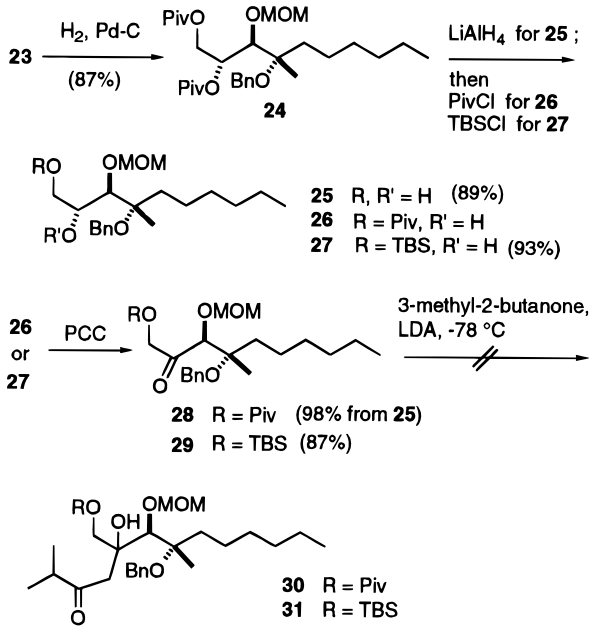
Scheme 4



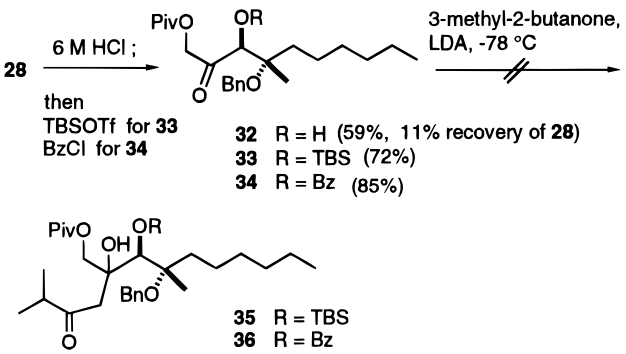
Next, our synthetic efforts were focused on the five-carbon elongation of di-*O*-pivaloyl ester **14**, which was prepared from **5** by per-*O*-pivaloylation (Scheme 4). Acid hydrolysis of **14** gave diol **15** as an anomeric mixture. Glycol cleavage of **15** with $NaIO_4$ gave an acyclic aldopentose **16**. By using the salt-free phosphorane prepared from pentyltriphenylphosphonium bromide with $NaNH_2$, the Wittig olefination of **16** gave the desired adduct **17**, albeit in 6% yield from **15**; the de-*O*-formyl derivative **21** of **17** was also obtained in 16% yield. Under other Wittig reactions carried out with a variety of bases, such as $KN[Si(Me)_3]_2$, *n*-BuLi, or $NaCH_2S(O)CH_3$, a complex mixture or the de-*O*-formyl derivative **18** of **16** was the predominant product. We also examined the Wittig reactions of other 3-*O*-protected aldehydes, the trimethylsilyl ether **19**, and the methoxymethyl (MOM) ether **20**. These two substrates **19** and **20** were prepared from **16** by selective deesterification of the formyl group with triethylamine followed by an appropriate protection procedure. The Wittig reaction of **19** with the pentylidene ylide in THF gave the *Z*-adduct **22** in 44% yield. Wittig olefination of the MOM ether **20** provided the *Z*-isomer **23** in 91% yield. The homogeneity of the *Z*-isomer was confirmed by ^1H NMR analysis ($J_{HC=CH}$ = 12.3 Hz). This improved Wittig olefination achieved using **20** may be due to the stability of the 3-*O*-MOM ether under the basic conditions used.

Since we found a practical route for installation of the side chain in **1**, our synthetic efforts were then focused on construction of the furan nucleus. Hydrogenation of the double bond in **23** in the presence of Pd on charcoal gave **24** (Scheme 5). Deprotection of the pivaloyl esters in **24** with $LiAlH_4$ followed by protection of the primary hydroxy group in the resulting diol **25** as the pivaloyl ester or the TBS ether gave **26** or **27.** The secondary

Scheme 5



Scheme 6

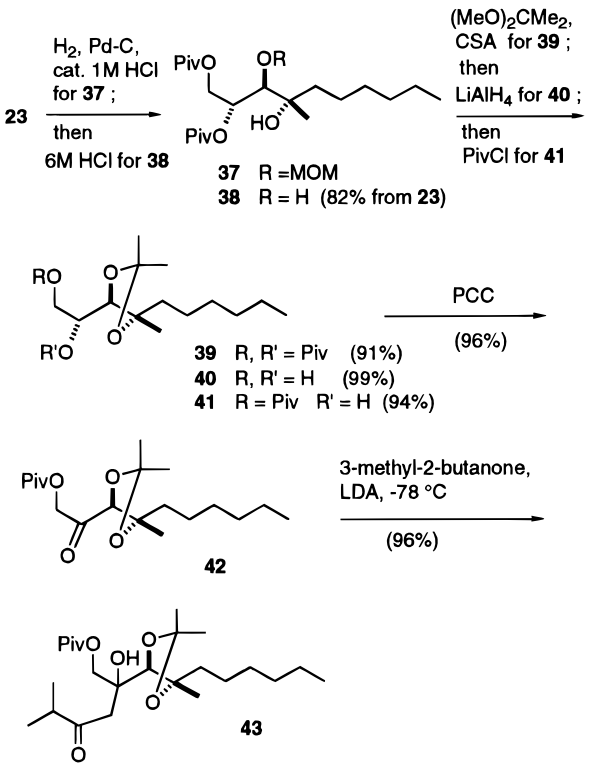


hydroxy groups in **26** and **27** were then oxidized with PCC to give two ketones **28** and **29**. In contrast to the above result which was obtained using ketone **6**, the aldol reaction of either **28** or **29** with the kinetic enolate of 3-methyl-2-butanone, which leads to **30** or **31**, did not take place. The starting ketone **28** or **29** was recovered almost quantitatively.

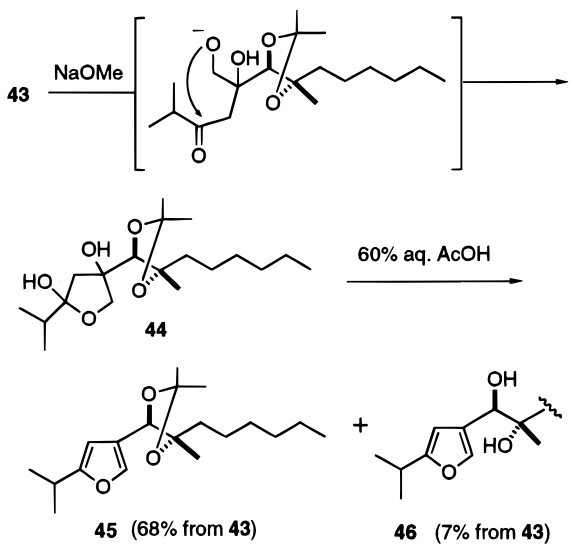
We prepared two other ketones, in which the 3-*O*-MOM group in **28** was replaced by a TBS group or a benzoyl group. These ketones **33** and **34** were prepared from **28** by deprotection of the MOM group followed by appropriate protection of the resulting **32** (Scheme 6). Again, neither **33** nor **34** gave the desired aldol adduct **35** or **36** in the reaction with the enolate of 3-methyl-2-butanone. We considered that the lack of reactivity in the aldol reaction observed in the case of **28**, **29**, **33**, or **34** might be a consequence of the less-restricted mobility in their acyclic structures. The long aliphatic side chain in these ketones may shield the carbonyl functionality from attack by the nucleophile.

To achieve the desired aldol reaction efficiently, we prepared a cyclic substrate **42**, which was expected to allow the attack of the nucleophile more readily. Ketone **42** is conformationally less flexible than the acyclic substrates **28**, **29**, **33**, and **34** due to its five-membered ring structure. The aldol reaction of **42** with the enolate of 3-methyl-2-butanone was investigated by taking this steric environment into consideration. Compound **42** was prepared from **23** straightforwardly (Scheme 7). Hydro-

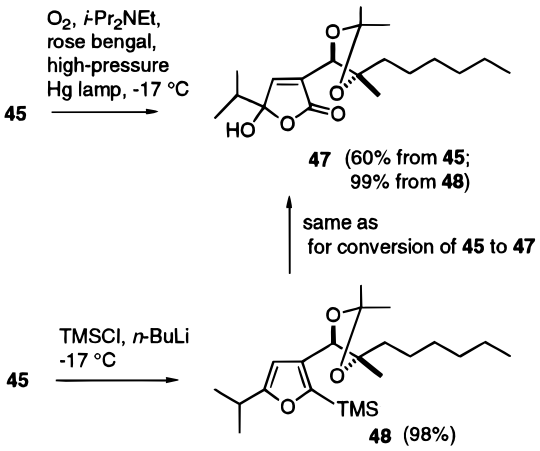
Scheme 7



Scheme 8



Scheme 9



genation of **23** in the presence of 1 M aqueous HCl in EtOH (1:60, v/v) gave **37**. Hydrogenolysis of the benzyl group occurred simultaneously. The MOM group was then hydrolyzed, and the resulting diol **38** was protected as the isopropylidene ketal to give **39** in a high overall yield from **23**. The pivaloyl groups in **39** were removed reductively to give diol **40**. Protection of the primary hydroxy group in **40** as the pivaloyl ester gave **41** in 93% yield from **39**. The aldol reaction of ketone **42**, prepared from **41** by PCC oxidation, with the kinetic enolate of 3-methyl-2-butanone proceeded cleanly to afford the desired aldol adducts **43** as a diastereomeric mixture in 96% yield. On the basis of the ^{1}H NMR analysis, the adducts **43** consist of two diastereomers in a 3:7 ratio. We could not determine the configuration of each diastereomer spectrally and used the mixture for the next step.

Formation of the furan nucleus from **43** was best achieved by the following procedure. Treatment of the aldol mixture **43** with NaOMe afforded tetrahydrofuran diol **44** as an inseparable diastereomeric mixture (Scheme 8). The reaction proceeded first via depivaloylation and then by attack of the carbonyl group by the resulting alkoxy anion, as depicted. Due to the instability of the cyclized product **44**, the ratio and stereochemical assignment of this mixture could not be determined. The crude reaction mixture was immediately exposed to 60% aqueous acetic acid at 60 °C for 1 h. After chromatographic separation on silica gel, the desired furan **45** was isolated in 68% yield, and the de-*O*-isopropylidene derivative **46** of **45** was obtained in 7% yield. Unfortunately, we could not identify optimal reaction conditions which provided **45** exclusively.

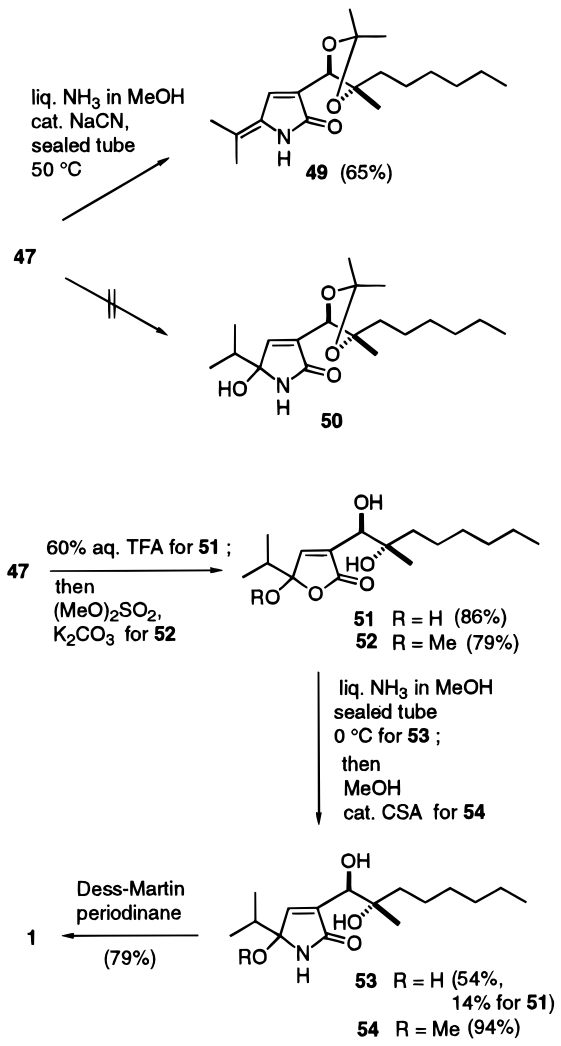
Transformation of furan **45** into the γ-hydroxy γ-lactone skeleton was investigated. A previous report[8] revealed that the addition of a singlet oxygen to some 3-alkylated furans under photochemical conditions efficiently afforded the corresponding γ-hydroxy γ-lactone derivatives. We expected that **45** could be converted to the desired γ-hydroxy γ-lactone **47** by similar procedures. In fact, when furan **45** was irradiated using a high-pressure mercury lamp under an oxygen atmosphere in the presence of a catalytic amount of rose bengal and equimolar diisopropylethylamine at −17 °C, **47** was obtained in 60% yield (Scheme 9). This product **47** was a diastereomerically single compound, however, we could not determine its structure unambiguously by ^{1}H NMR analysis. The yield of **47** was improved by the introduction of a trimethylsilyl group at the α-position of the furan nucleus in **45**. This tendency was obvious based on previous reports.[9] Thus, exposure of **45** to *n*-BuLi followed by addition of trimethylsilyl chloride gave the trimethylsilylated furan **48** in 98% yield. Photochemical oxidation of **48** under the same conditions used for **45** provided **47** nearly quantitatively.

The final stage of the total synthesis of **1** was transformation of the γ-lactone structure in **47** into a lactam structure and subsequent oxidation of the α-hydroxyl group in the side chain. When the γ-lactone **47** was

(8) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773, and references cited therein.

(9) (a) Adam. W.; Rodriquez, A. *Tetrahedron Lett.* **1981**, *22*, 3505. (b) Katsumura, S.; Hori, K.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 4625. Also, see ref 8.

Scheme 10



heated as a solution of liquid ammonia and MeOH at 50 °C in the presence of a catalytic amount of NaCN in a sealed tube, lactone−lactam transformation took place smoothly (Scheme 10). However, the product **49** isolated in 65% yield was the dehydrated form of the expected γ-lactam **50**. After further experiments, we found that exposure of methyl ketal **52** to liquid ammonia in MeOH resulted in the desired lactone−lactam transformation efficiently. The substrate **52** was prepared from **47** by hydrolysis with 60% aqueous TFA followed by methyl ketalization of the resulting de-*O*-isopropylidene derivative **51**.[10] Interestingly, methyl ketalization of **51** was possible only under basic conditions using dimethyl sulfate in the presence of K_2CO_3. The methyl ketal **52** was treated with liquid ammonia in MeOH, as in the case of **47**, in the absence of NaCN. The γ-hydroxy γ-lactam **53** was obtained in 54% yield. We did not expect that the methyl ketal moiety in **52** would be converted to a hemiketal form in **53** under these reaction conditions. The formation of **53** can be explained by assuming that the attack of the lactone carbonyl in **52** by ammonia opens the γ-lactone ring, and the methoxy group in this intermediate leaves to give the γ-keto-α,β-unsaturated amide. This acyclic intermediate then spontaneously cyclizes to give the γ-hydroxy γ-lactam **53**. Along with the formation of **53**, 14% of **51** was also isolated from the reaction mixture. The mechanism of the formation of **51** is unclear;[11] however, the minor product **51** could be reused to produce **53**. The hemiketal **53** was converted to ketal **54** under usual acidic conditions. The resulting methyl ketal **54** existed in a 1:1 diastereomeric mixture with regard to the ketal carbons. Finally, the secondary hydroxy group in **54** was oxidized by the Dess−Martin periodinane[12] to provide PI-091 (**1**) in 79% yield. Other oxidation conditions, such as $BaMnO_4$ in CH_2Cl_2 or PDC/MS 4A in CH_2Cl_2, gave a complex mixture. A 1:1 diastereomeric mixture of synthetic **1** was identical to a natural sample by spectral (^{1}H, ^{13}C NMR, IR) and TLC comparisons. Furthermore, $[\alpha]_D$ of synthetic **1** verified the absolute configuration of natural PI-091, as depicted in Figure 1. The IC_{50} of synthetic **1** for rabbit platelet aggregation inhibition was confirmed to be similar to that of a natural specimen by a parallel biological assay.

In conclusion, we completed the total synthesis of PI-091 (**1**) in its natural form. Our synthesis was characterized by the following points: (1) The high-yield aldol reaction of suitably protected 1,3,4-trihydroxy-4-methyldecan-2-one **42** with the kinetically generated enolate of 3-methyl-2-butanone was realized to give **43**. The intermediate **43**, which possesses all of the required carbons in **1**, was efficiently converted to 2,4-disubstituted furan **45**. (2) The photochemical addition of a singlet oxygen to the silylated furan **48** derived from **45** gave the fully functionalized γ-hydroxy γ-lactone **47** in high yield. (3) Lactone−lactam transformation was effectively achieved by exposing an advanced intermediate **52** derived from **47** to liquid ammonia. Finally, the total synthesis was completed from the resulting γ-lactam **53** through the Dess−Martin oxidation of the secondary hydroxy group in the side chain.

Experimental Section

Melting points are uncorrected. Specific rotations were measured in a 10-mm cell. ^{1}H NMR spectra were recorded at 90 MHz or 270 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 67.5 MHz or 100 MHz in $CDCl_3$ solution.

Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 GF_{254} (Merck). Crude reaction mixtures and extractive materials were purified by chromatography on silica gel 60 K070 (Katayama Chemicals).

Unless otherwise specified, reactions were carried out at room temperature (rt). Organic extracts were dried over anhydrous Na_2SO_4. Reagents and solvents were removed by concentration in vacuo using an evaporator with bath at 35−45 °C.

Solvents were dried (drying reagent in parenthesis) and distilled prior to use: tetrahydrofuran = THF ($LiAlH_4$ and then Na/benzophenone ketyl), *N*,*N*-dimethylformamide = DMF ($MgSO_4$), CH_2Cl_2 (CaH_2), benzene (CaH_2), dimethyl sulfoxide = DMSO (CaH_2), pyridine (NaOH), and toluene (CaH_2).

3-*O*-Benzyl-1,2-*O*-isopropylidene-3-*C*-methyl-5,6-di-*O*-pivaloyl-α-D-allofuranose (14). To a cold (0 °C) stirred solution of **5**[6,7] (9.64 g, 30.0 mmol) in pyridine (100 mL) was added dropwise pivaloyl chloride (11.1 mL, 89.2 mmol). After stirring for 9 h, pivaloyl chloride (3.7 mL, 29.5 mmol) and 4-(dimethylamino)pyridine (DMAP) (363 mg, 3.0 mmol) were

(10) We also subjected the hemiketal **51** to the γ-lactone γ-lactam transformation conditions used for **47**. Under these conditions, a product which was the dehydrated form of the expected γ-lactam was obtained as a major product.

(11) It is likely that the methoxide anion generated in liquid ammonia in MeOH attacked the lactone carbonyl in **52**, then opened the γ-lactone ring to leave an acyclic γ-keto-α,β-unsaturated methyl ester after departure of the methoxy group. This intermediate recyclized to form the γ-lactone **51**.

(12) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

added. The mixture was stirred for an additional 23 h, diluted with EtOAc (1 L), and washed with saturated aqueous $NaHCO_3$ (1 L) and brine (1 L × 2). The organic layer was dried and concentrated in vacuo. The residue was passed through a short column of silica gel (EtOAc/hexane, 1:10) to give **14** (14.8 g) as a colorless oil, which was used in the next step. An analytical sample was obtained by repeated chromatography on silica gel: TLC, R_f 0.58 (EtOAc/hexane, 1:3); mp 78−80 °C; $[\alpha]^{19}_D$ +51.3° (*c* 1.40, $CHCl_3$); IR (neat) 2990, 1740, 1480, 1460, 1400 cm^{-1}; ^1H NMR (270 MHz) δ 1.02, 1.17 (2 s, each 9 H), 1.31, 1.35 (2 s, each 3 H), 1.61 (s, 3 H), 4.09 (dd, J = 6.2, 11.9 Hz, 1 H), 4.24 (d, J = 8.6 Hz, 1 H), 4.37 (d, J = 3.7 Hz, 1 H), 4.47−4.59 (m, 3 H), 5.27 (ddd, J = 2.6, 6.2, 8.6 Hz, 1 H), 5.71 (d, J = 3.7 Hz, 1 H), 7.25−7.38 (m, 5 H). Anal. Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19. Found: C, 65.83, H, 8.15.

3-*O*-Benzyl-3-*C*-methyl-5,6-di-*O*-pivaloyl-α-D-allofuranose (15). A solution of **14** (14.8 g) in 60% aqueous CF_3COOH (200 mL) was stirred for 6.5 h. The solution was neutralized by addition of 10 M aqueous NaOH, diluted with EtOAc (1 L), and washed with H_2O (500 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give a 5:1 anomeric mixture **15** (12.1 g, 90% from **5**) as an inseparable colorless oil: TLC, R_f 0.15 (EtOAc/hexane, 1:3); IR (neat) 3490, 2970, 1730, 1480 cm^{-1}; ^1H NMR (270 MHz) δ 1.19 (s, 9 H × 2), 1.45 (s, 5/6 × 3 H), 1.51 (s, 1/6 × 3 H), 3.80 (d, J = 2.2 Hz, 1/6 × 1 H), 3.82 (d, J = 4.0 Hz, 5/6 × 1 H), 4.07−4.59 (m, 5 H), 5.08 (ddd, J = 2.6, 5.9, 8.8 Hz, 5/6 × 1 H), 5.18−5.24 (m, 1/6 × 1 H), 5.22 (d, J = 4.0 Hz, 5/6 × 1 H), 5.30 (d, J = 2.2 Hz, 1/6 × 1 H), 7.26−7.40 (m, 5 H).

(2*R*,3*R*,4*R*)-2-(Benzyloxy)-3-(methoxymethoxy)-2-methyl-4,5-bis(pivaloyloxy)pentanal (20). To a cold (0 °C) stirred solution of **15** (2.92 g, 6.5 mmol) in MeOH (60 mL) was added an aqueous solution (40 mL) of $NaIO_4$ (5.52 g, 25.8 mmol). After stirring for 3 h, the solution was diluted with saturated brine (200 mL) and extracted with CH_2Cl_2 (150 mL × 3). The combined extracts were dried and concentrated in vacuo to give crude **16** (3.25 g), which was used in the next step without further purification, as a colorless oil: TLC, R_f 0.53 (EtOAc/hexane, 1:3); IR (neat) 2960, 1735, 1480, 1460, 1390, 1360 cm^{-1}; ^1H NMR (90 MHz) δ 1.14, 1.19 (2 s, each 9 H), 1.42 (s, 3 H), 4.05 (dd, J = 5.0, 13.0 Hz, 1 H), 4.52 (dd, J = 3.0, 13.0 Hz, 1 H), 4.64 (s, 2 H), 5.30−5.48 (m, 1 H), 5.68 (dd, J = 1.0, 7.0 Hz, 1 H), 7.33 (s, 5 H), 8.17 (d, J = 1.0 Hz, 1 H), 9.62 (s, 1 H).

A solution of crude **16** (3.25 g) in MeOH (60 mL) was stirred in the presence of Et_3N (2.7 mL, 19.4 mmol) for 1 h and concentrated in vacuo to give crude **18** (3.00 g), which was used in the next step without purification, as a colorless oil: TLC, R_f 0.58 (EtOAc/hexane, 1:2); IR (neat) 3480, 2980, 1740, 1480, 1400, 1360 cm^{-1}; ^1H NMR (270 MHz) δ 1.16, 1.20 (2 s, each 9 H), 1.52 (s, 3 H), 2.94 (d, J = 8.4 Hz, 1 H), 3.87 (t, J = 8.4 Hz, 1 H), 4.36 (dd, J = 3.7, 12.5 Hz, 1 H), 4.44 (dd, J = 2.6, 12.5 Hz, 1 H), 4.63 (s, 2 H), 5.22 (ddd, J = 2.6, 3.7, 8.4 Hz, 1H), 7.26−7.36 (m, 5 H), 9.63 (s, 1 H).

To a stirred solution of crude **18** (3.00 g) in CH_2Cl_2 (60 mL) were added *i*-Pr_2NEt (22.5 mL, 129.0 mmol) and methyl chloromethyl ether (MOMCl) (4.9 mL, 64.5 mmol). The solution was heated under reflux for 16 h, and *i*-Pr_2NEt (9.0 mL) and MOMCl (2.5 mL) were added. After heating under reflux for an additional 4 h, the solution was diluted with EtOAc (250 mL) and washed with 0.2 M HCl solution (200 mL × 2), saturated aqueous $NaHCO_3$ (200 mL), and saturated brine (200 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to give **20** (2.36 g, 78% from **15**) as a colorless oil, and 531 mg (19% from **15**) of **18** was recovered. **20**: TLC, R_f 0.38 (EtOAc/hexane, 1:4); $[\alpha]^{26}_D$ −5.4° (*c* 1.27, $CHCl_3$); IR (neat) 2970, 1740, 1480, 1400, 1370 cm^{-1}; ^1H NMR (270 MHz) δ 1.17, 1.18 (2 s, each 9 H), 1.49 (s, 3 H), 3.37 (s, 3 H), 4.08 (d, J = 4.9 Hz, 1 H), 4.19 (dd, J = 6.8, 12.7 Hz, 1 H), 4.48, 4.65 (ABq, J = 11.7 Hz, each 1H), 4.53 (dd, J = 2.4, 12.7 Hz, 1 H), 4.63, 4.80 (ABq, J = 6.6 Hz, each 1 H), 5.42 (ddd, J = 2.4, 4.9, 6.8 Hz, 1 H), 7.24−7.35 (m, 5 H), 9.60 (s, 1 H); HRMS calcd for $C_{23}H_{33}O_7$ ($M^+ - CH_2OCH_3$) m/z 421.2224, found 421.2210.

(2*R*,3*R*,4*S*,5*Z*)-4-(Benzyloxy)-3-(methoxymethoxy)-4-methyl-1,2-bis(pivaloyloxy)-5-decene (23). The following reaction was carried out under Ar. To a stirred solution of **20** (2.36 g, 5.1 mmol) in THF (60 mL) was added $Ph_3P{=}CH(CH_2)_3CH_3$ [1 M solution in THF, 15.0 mL, 15.0 mmol: this ylide solution was prepared as follows; a mixture of 33.1 g (80.1 mmol) of $CH_3(CH_2)_4P^+Ph_3Br^-$ and sodium amide (3.12 g, 80.0 mmol) in THF (80 mL) was heated under reflux for 4.5 h, the solution was cooled to rt, and the supernatant solution was used for the Wittig reaction]. The solution was stirred at rt while 15.0 mL of the ylide solution was added after 10 min and 20 min (total 30.0 mL). The solution was stirred for an additional 30 min, quenched by adding a small amount of H_2O, diluted with EtOAc (300 mL), and washed with saturated aqueous NH_4Cl (150 mL) and saturated brine (150 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to give **23** (2.39 g, 91%) as a colorless oil: TLC, R_f 0.61 (EtOAc/hexane, 1:5); $[\alpha]^{24}_D$ +16.0° (*c* 1.17, $CHCl_3$); IR (neat) 2950, 1730, 1480, 1460, 1400 cm^{-1}; ^1H NMR (270 MHz) δ 0.82 (t, J = 7.2 Hz, 3 H), 1.15, 1.19 (2 s, each 9 H), 1.29−1.32 (m, 4 H), 1.52 (s, 3 H), 2.21−2.24 (m, 2 H), 3.40 (s, 3 H), 3.79 (d, J = 1.5 Hz, 1 H), 4.31 (dd, J = 9.2, 12.3 Hz, 1 H), 4.45, 4.53 (ABq, J = 12.3 Hz, each 1 H), 4.63 (dd, J = 2.2, 12.3 Hz, 1 H), 4.73, 4.80 (ABq, J = 6.6 Hz, each 1 H), 5.27 (d, J = 12.1 Hz, 1 H), 5.57−5.67 (m, 2 H), 7.29−7.32 (m, 5 H); ^{13}C NMR (100 MHz) δ 13.9, 21.9, 22.5, 27.09, 27.14, 28.2, 31.9, 38.6, 38.7, 56.5, 64.5, 64.7, 72.6, 80.5, 83.9, 97.8, 126.91, 126.94, 128.1, 130.1, 135,4, 139.2, 177.2, 178.2; HRMS, calcd for $C_{30}H_{47}O_7$ ($M^+ - H$) m/z 519.3318, found 519.3292.

(2*R*,3*R*,4*S*)-3-(Methoxymethoxy)-4-methyl-1,2-bis(pivaloyloxy)-4-decanol (37). A solution of **23** (3.09 g, 5.9 mmol) in EtOH (60 mL) was hydrogenated in the presence of 10% Pd on charcoal (300 mg) under an atmosphere of H_2 for 3 h. A 1 M aqueous HCl (1 mL) solution was then added to the mixture. The hydrogenation was continued for 14 h, and an additional 700 mg of the catalyst was added. The hydrogenation was continued for an additional 3 h. The catalyst was removed by filtration through a pad of Celite and washed well with EtOH. The combined filtrate and washing were concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:6) to give **37** (2.62 g, >100%) as a colorless oil, which was used in the next step without further purification: TLC, R_f 0.36 (EtOAc/hexane, 1:4); $[\alpha]^{26}_D$ +2.7° (*c* 1.51, $CHCl_3$); IR (neat) 3520, 2960, 1730, 1480, 1460, 1400 cm^{-1}; ^1H NMR (270 MHz) δ 0.89 (t, J = 6.4 Hz, 3 H), 1.17, 1.21 (2 s, each 9 H), 1.23 (s, 3 H), 1.11−1.62 (m, 10 H), 3.45 (s, 3 H), 3.55 (d, J = 2.2 Hz, 1 H), 4.22 (dd, J = 8.4, 12.5 Hz, 1 H), 4.60 (dd, J = 2.2, 12.5 Hz, 1 H), 4.71, 4.83 (ABq, J = 6.4 Hz, each 1 H), 5.37 (dt, J = 2.2, 8.4 Hz, 1 H); HRMS, calcd for $C_{23}H_{43}O_6$ ($M^+ - OH$) m/z 415.3056, found 415.3052.

(2*R*,3*R*,4*S*)-4-Methyl-1,2-bis(pivaloyloxy)-3,4-decanediol (38). A solution of **37** (2.62 g) in 6 M aqueous HCl (100 mL) and THF (100 mL) was stirred for 6 h. The solution was neutralized with 10 M aqueous NaOH and concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (200 mL) and saturated brine (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (200 mL × 2). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:7) to give **38** (1.93 g, 82% from **23**) as a colorless oil, and 373 mg (14%) of **37** was recovered. **38**: TLC, R_f 0.20 (EtOAc/hexane, 1:5); $[\alpha]^{27}_D$ +5.1° (*c* 0.85, $CHCl_3$); IR (neat) 3490, 2960, 2940, 1720, 1480, 1460, 1400 cm^{-1}; ^1H NMR (270 MHz) δ 0.89 (t, J = 6.4 Hz, 3 H), 1.20, 1.22 (2 s, each 9 H), 1.23 (s, 3 H), 1.12−1.64 (m, 10 H), 3.57 (d, J = 5.1 Hz, 1 H), 4.36 (dd, J = 6.6, 12.5 Hz, 1 H), 4.55 (dd, J = 2.8, 12.5 Hz, 1 H), 5.18 (ddd, J = 2.8, 5.1, 6.6 Hz, 1 H); ^{13}C NMR (100 MHz) δ 14.1, 22.6, 23.2, 24.2, 27.06, 27.14, 29.9, 31.8, 37.2, 38.8, 63.1, 72.1, 73.9, 76.1, 177.5, 178.7; HRMS, calcd for $C_{21}H_{39}O_5$ ($M^+ - OH$) m/z 371.2817, found 371.2795.

(2*R*,3*R*,4*S*)-3,4-(Isopropylidenedioxy)-4-methyl-1,2-bis(pivaloyloxy)decane (39). To a cold (0 °C) stirred solution of **38** (2.17 g, 5.6 mmol) in acetone (40 mL) was added

dimethoxypropane (5.5 mL, 44.6 mmol) and camphorsulfonic acid (CSA) (130 mg, 0.56 mmol). The mixture was stirred for 23 h, while 130 mg, 390 mg, and 130 mg of CSA was added after 3, 3.5, and 4 h, respectively. The solution was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (100 m L). The aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layers were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:40) to give **39** (2.17 g, 91%) as a colorless oil: TLC, R_f 0.76 (EtOAc/hexane, 1:5); $[\alpha]^{22}_D$ −19.0° (*c* 1.05, $CHCl_3$); IR (neat) 2980, 1740, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.87 (t, J = 6.4 Hz, 3 H), 1.20, 1.21 (2 s, each 9 H), 1.34, 1.39 (2 s, each 3 H), 1.11−1.46 (m, 13 H), 3.95 (d, J = 9.7 Hz, 1 H), 4.16 (dd, J = 4.6, 12.1 Hz, 1 H), 4.56 (dd, J = 2.2, 12.1 Hz, 1 H), 5.16 (ddd, J = 2.2, 4.6, 9.7 Hz, 1 H); HRMS, calcd for $C_{23}H_{41}O_6$ ($M^+ - CH_3$) m/z 413.2900, found 413.2883.

(2*R*,3*R*,4*S*)-3,4-(Isopropylidenedioxy)-4-methyl-1,2-decanediol (40). To a cold (0 °C) stirred solution of **39** (1.35 g, 3.2 mmol) in THF (30 mL) was added $LiAlH_4$ (240 mg, 6.3 mmol). After stirring for 30 min, the solution was quenched with H_2O (0.3 mL), and aqueous NaOH (15 wt %, 0.3 mL) and H_2O (0.9 mL) were added successively. The entire mixture was stirred for 30 min, and the resulting solids were removed by filtration through a pad of Celite and washed well with EtOAc (300 mL). The combined filtrate and washings were washed with H_2O (150 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to give **40** (813 mg, 99%) as a colorless oil: TLC, R_f 0.24 (EtOAc/hexane, 1:2); $[\alpha]^{24}_D$ −23.0° (*c* 1.38, $CHCl_3$); IR (neat) 3400, 2970, 1455 cm^{-1}; ^1H NMR (270 MHz) δ 0.89 (t, J = 6.6 Hz, 3 H), 1.30−1.64 (m, 19 H), 2.54, 2.70 (2 br s, each 1H), 3.64 (d, J = 8.8 Hz, 1 H), 3.69−3.89 (m, 3 H); HRMS, calcd for $C_{13}H_{25}O_4$ ($M^+ - CH_3$) m/z 245.1751, found 245.1751.

(2*R*,3*R*,4*S*)-3,4-(Isopropylidenedioxy)-4-methyl-1-(pivaloyloxy)-2-decanol (41). To a cold (0 °C) stirred solution of **40** (813 mg, 3.1 mmol) in pyridine (20 mL) was added pivaloyl chloride (0.42 mL, 3.4 mmol). After stirring for 80 min, the solution was diluted with EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated brine (50 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:15) to give **41** (1.02 g, 94%) as a colorless oil: TLC, R_f 0.45 (EtOAc/hexane, 1:5); $[\alpha]^{22}_D$ −12.0 ° (*c* 1.34, $CHCl_3$); IR (neat) 3500, 2940, 1720, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.89 (t, J = 6.6 Hz, 3 H), 1.24 (s, 9 H), 1.30−1.50 (m, 16H), 1.39 (s, 3 H), 3.60 (d, J = 9.2 Hz, 1 H), 3.92−3.97 (m, 1 H), 4.19 (dd, J = 6.2, 11.7 Hz, 1 H), 4.40 (dd, J = 2.2, 11.7 Hz, 1 H); HRMS, calcd for $C_{18}H_{33}O_5$ ($M^+ - CH_3$) m/z 329.2326, found 329.2330.

(3*S*,4*S*)-3,4-(Isopropylidenedioxy)-4-methyl-1-(pivaloyloxy)-2-decanone (42). To a cold (0 °C) stirred solution of **41** (1.02 g, 3.0 mmol) in CH_2Cl_2 (20 mL) were added PCC (1.91g, 8.9 mmol) and molecular sieves (4 Å, 1.0 g). The mixture was stirred for 20 h, and the solvent was removed by evaporation. The residue was transferred to a short column of silica gel with Et_2O, and the column was eluted with excess Et_2O. The ethereal eluate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to give **42** (969 mg, 96%) as a colorless oil: TLC, R_f 0.67 (EtOAc/hexane, 1:5); $[\alpha]^{22}_D$ −82.0° (*c* 1.58, $CHCl_3$); IR (neat) 2990, 1740, 1480 cm^{-1}; ^1H NMR (270 MHz) δ 0.87 (t, J = 6.6 Hz, 3 H), 1.27 (s, 9 H), 1.37, 1.40, 1.49 (3 s, each 3 H), 1.27−1.50 (m, 10 H), 4.24 (s, 1 H), 4.92, 5.01 (ABq, J = 18.0 Hz, each 1H); ^{13}C NMR (100 MHz) δ 14.0, 22.5, 23.0, 23.9, 26.8, 27.2, 28.1, 28.8, 29.7, 31.6, 31.7, 35.3, 38.7, 67.5, 83.5, 87.7, 108.9, 177.7, 201.5; HRMS, calcd for $C_{19}H_{35}O_5$ (M^+ + H) m/z 343.2482, found 343.2476.

Mixture of (5*R* and *S*,6*S*,7*S*)-5-Hydroxy-6,7-(isopropylidenedioxy)-2,7-dimethyl-5-[(pivaloyloxy)methyl]-3-tridecanone (43). The following reaction was carried out under Ar. To a cold (-78 °C) stirred solution of LDA in THF (2 mL), prepared by mixing *i*-Pr_2NH (0.83 mL, 5.9 mmol) and *n*-BuLi (1.60 M solution in hexane, 3.60 mL, 5.9 mmol) at 0 °C, was added dropwise 3-methyl-2-butanone (0.63 mL, 5.9 mmol). After stirring at −78 °C for 40 min, a solution of **42** (505 mg, 1.5 mmol) in THF (10 mL) was added. The solution was stirred at -78 °C for 15 min, diluted with saturated aqueous NH_4Cl (100 mL), and extracted with CH_2Cl_2 (100 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to give **43** (604 mg, 96%) as an inseparable colorless oil: TLC, R_f 0.59 (EtOAc/hexane, 1:5); IR (neat) 3450, 2960, 1730, 1480, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.85−0.90 (m, 3 H), 1.09−1.14 (m, 6 H), 1.22 (s, 9 H), 1.26−1.32 (m, 16 H), 1.41 (s, 3 H × 3/10), 1.42 (s, 3 H × 7/10), 2.58−2.67 (m, 1 H), 2.75, 2.98 (ABq, J = 16.7 Hz, each 1 H × 7/10), 2.77, 3.00 (ABq, J = 17.4 Hz, each 1 H × 3/10), 3.66 (s, 1 H × 7/10), 3.80 (s, 1 H × 3/10), 3.97 (s, 1 H × 3/10), 4.10, 4.16 (ABq, J = 11.4 Hz, each 1 H × 7/10), 4.21, 4.37 (ABq, J = 11.5 Hz, each 1 H × 3/10), 4.53 (s, 1 H × 7/10); HRMS, calcd for $C_{23}H_{41}O_6$ ($M^+ - CH_3$) m/z 413.2901, found 413.2902.

2-Isopropyl-4-[(1*R*,2*S*)-1,2-(isopropylidenedioxy)-2-methyloctyl]furan (45) and Its De-*O*-isopropylidene Form (46). To a cold (0 °C) stirred solution of **43** (992 mg, 2.3 mmol) in MeOH (15 mL) was added dropwise MeONa (1.0 M solution in MeOH, 13.9 mL, 13.9 mmol). After stirring for 4 h, the solution was diluted with saturated aqueous NH_4Cl (200 mL) and extracted with CH_2Cl_2 (200 mL × 3). The combined extracts were dried and concentrated in vacuo to give crude **44**, which was immediately used in the next step.

The residue was dissolved in 60% aqueous acetic acid (20 mL), and the solution was stirred at 60 °C for 70 min and then concentrated in vacuo with the aid of toluene and EtOH. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to give **45** (486 mg, 68%) and **46** (44 mg, 7%) as colorless oils. **45**: TLC, R_f 0.91 (EtOAc/hexane, 1:4); $[\alpha]^{25}_D$ −58.7° (*c* 1.02, $CHCl_3$); IR (neat) 2960, 2940, 2860, 1550, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.86 (t, J = 6.6 Hz, 3 H), 1.23 (d, J = 6.6 Hz, 6 H), 1.27 (s, 3 H), 1.41, 1.49 (2 s, each 3 H), 1.22−1.60 (m, 10 H), 2.91 (heptet, J = 6.6 Hz, 1 H), 4.70 (s, 1 H), 5.97 (s, 1 H), 7.29 (s, 1 H); ^{13}C NMR (100 MHz) δ 14.1, 21.01, 21.05, 22.6, 22.7, 23.3, 26.9, 27.8, 28.4, 29.9, 31.9, 35.7, 80.3, 82.6, 102.2, 107.0, 121.1, 138.0, 162.3; HRMS, calcd for $C_{19}H_{32}O_3$ ($M^{+)}$ m/z 308.2349, found 308.2355. **46**: TLC, R_f 0.16 (EtOAc/hexane, 1:4); $[\alpha]^{27}_D$ −13.1° (*c* 0.95, $CHCl_3$); IR (neat) 3430, 2960, 2930, 1540, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.87 (t, J = 6.6 Hz, 3 H), 1.23 (s, 3 H), 1.23 (d, J = 7.0 Hz, 6 H), 1.23−1.55 (m, 10 H), 1.88 (br s, 1 H), 2.18 (br s, 1 H), 2.90 (heptet, J = 7.0 Hz, 1 H), 4.43 (s, 1 H), 6.02 (s, 1 H), 7.27 (s, 1 H).

4-Isopropyl-4-hydroxy-2-[(1*R*,2*S*)-1,2-(isopropylidenedioxy)-2-methyloctyl]-2-buten-4-olide (47). A solution of **48** (see below) (419 mg, 1.1 mmol) and *i*-Pr_2NEt (0.19 mL, 1.1 mmol) in CH_2Cl_2 (18 mL) containing 1.8 mg of rose bengal was irradiated by a high-pressure mercury lamp under 1 atm of O_2 at −17 °C (ice−NaCl bath) for 20 min. The solution was concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4) to give **47** (370 mg, 99%) as a colorless oil: TLC, R_f 0.27 (EtOAc/hexane, 1:4); $[\alpha]^{23}_D$ −61.0° (*c* 0.98, $CHCl_3$); IR (neat) 3400, 2930, 1760, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.87 (t, J = 6.6 Hz, 3 H), 1.04 (d, J = 6.8 Hz, 6 H), 1.23−1.28, 1.30−1.39, 1.40, 1.47 (2 m, s, s, 10 H, 3 H, 6 H), 2.20 (heptet, J = 6.8 Hz, 1 H), 4.65 (d, J = 2.0 Hz, 1 H), 7.15 (d, J = 2.0 Hz, 1 H); HRMS, calcd for $C_{18}H_{29}O_5$ ($M^+ - CH_3$) m/z 325.2013, found 325.1981.

5-Isopropyl-3-[(1*R*,2*S*)-1,2-(isopropylidenedioxy)-2-methyloctyl]-2-trimethylsilylfuran (48). The following reaction was carried out under Ar. To a cold (−17 °C) stirred solution of **45** (347 mg, 1.12 mmol) in THF (7 mL) was added *n*-BuLi (1.66 M solution in hexane, 4.1 mL, 6.8 mmol). After stirring at −17 °C for 80 min, chlorotrimethylsilane (0.85 mL, 6.1 mmol) and triethylamine (0.85 mL) were added. The resulting solution was stirred at −17 °C for 10 min, quenched with H_2O (1 mL), diluted with EtOAc (40 mL), and washed with saturated brine (20 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:60) to give **48** (419 mg, 98%) as a colorless oil: TLC, R_f 0.51 (EtOAc/hexane, 1:16); $[\alpha]^{20}_D$ −55.7° (*c* 0.40, $CHCl_3$); IR (neat) 2960, 2940, 1600, 1520, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.29 (s, 9

H), 0.87 (t, J = 6.6 Hz, 3 H), 1.15−1.56 (m, 10 H), 1.23, 1.24 (2 d, J = 7.0 Hz, each 3 H), 1.27 (s, 3 H), 1.39, 1.51 (2 s, each 3 H), 2.91 (heptet, J = 6.6 Hz, 1 H), 4.81 (s, 1 H), 6.03 (d, J = 0.7 Hz, 1H); HRMS, calcd for $C_{22}H_{40}O_3Si$ (M^+) m/z 380.2744, found 380.2751.

Inseparable Mixture of (4*R* and *S*)-4-Isopropyl-4-hydroxy-2-[(1*R*,2*S*)-1,2-dihydroxy-2-methyloctyl]-2-buten-4-olide (51). A solution of **47** (370 mg, 1.09 mmol) in 60% aqueous TFA (7 mL) was stirred at 0 °C for 13 h. The solution was neutralized by addition of 10 M aqueous NaOH, diluted with H_2O (80 mL), and extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to give **51** (280 mg, 86%) as colorless crystals, and 13.5 mg (4%) of **47** was recovered. **51**, mp 123−124 °C: TLC, R_f 0.16 (EtOAc/hexane, 1:2); $[\alpha]^{27}_D$ −10.9 ° (c 0.82, $CHCl_3$); IR (neat) 3400, 2960, 2930, 1750, 1470 cm^{-1}; ^1H NMR (270 MHz) δ 0.87 (t, J = 6.4 Hz, 3 H), 1.00−1.04 (m, 6 H), 1.22−1.40 (m, 13 H), 2.18 (heptet, J = 6.4 Hz, 1 H), 2.86, 3.54, 3.64, 3.88 (each br s, each 0.5 H), 4.29 (br s, 1 H), 5.13 (br s, 0.5 H), 5.24 (br s, 0.5 H), 7.14 (s, 0.5 H), 7.19 (s, 0.5 H); ^{13}C NMR (100 MHz) δ 14.0, 16.45, 16.55, 17.0, 17.1, 21.8, 22.5, 22.6, 23.1, 23.3, 29.7, 29.8, 31.7, 34.9, 35.0, 37.8, 39.2, 71.7, 72.4, 74.8, 75.1, 101.0, 110.1, 110.3, 135.1, 135.6, 150.2, 151.0, 172.1, 172.3; HRMS, calcd for $C_{16}H_{26}O_4$ ($M^+ - H_2O$) m/z 282.1830, found 282.1835.

4-Isopropyl-2-[(1*R*,2S)-1,2-dihydroxy-2-methyloctyl]-4-methoxy-2-buten-4-olide (52). To a cold (0 °C) stirred solution of **51** (115 mg, 0.38 mmol) in 2-butanone (3 mL) were added dimethyl sulfate (54 μL, 0.57 mmol) and potassium carbonate (79.5 mg, 0.58 mmol). After stirring for 3.5 h, the solution was diluted with saturated brine (40 mL) and extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give **52** (94.3 mg, 79%) as colorless crystals, and 17.4 mg (15%) of **51** was recovered. Compound **52** was a diastereomerically single isomer with regard to C-4 based on ^1H NMR: mp 76−78 °C: $[\alpha]^{26}_D$ +39.1° (c 1.26, $CHCl_3$); IR (neat) 3500, 2920, 2850, 1700, 1630, 1460, 1440, 1420 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, J = 6.6 Hz, 3 H), 1.14, 1.15 (2 d, J = 7.0 Hz, each 3 H), 1.20 (s, 3 H), 1.25−1.60 (m, 10 H), 2.29 (br s, 1 H), 2.69 (heptet, J = 7.0 Hz, 1 H), 3.08 (br s, 1 H), 3.76 (s, 3 H), 4.27 (br s, 1 H), 6.57 (d, J = 1.1 Hz, 1 H); HRMS, calcd for $C_{17}H_{30}O_5$ (M^+ + H) m/z 315.2170, found 315.2170.

Inseparable Mixture at C-4 of 4-Isopropyl-4-hydroxy-2-[(1*R*,2*S*)-1,2-dihydroxy-2-methyloctyl]-2-butene-4-lactam (53). A solution of **52** (46 mg, 0.15 mmol) in MeOH (3 mL) and liquid ammonia (1 mL) was stirred in a sealed glass tube at 0 °C for 1 h. The solution was quenched with saturated aqueous NH_4Cl (1 mL) at 0 °C, diluted with saturated aqueous NH_4Cl (20 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (acetone/toluene, 1:4) to give **53** (24 mg, 54%) as a colorless oil and **51** (6.5 mg, 14%). **53**: TLC, R_f 0.43 (acetone/toluene, 1:1); $[\alpha]^{26}_D$ -5.3° (c 1.10, $CHCl_3$); IR (neat) 3350, 2960, 2920, 1700, 1680, 1640 cm^{-1}; ^1H NMR (270 MHz) δ 0.84−0.90 (m, 3 H), 0.96−1.01 (m, 6 H), 1.18−1.49, 1.64−1.86 (2m, total 13 H), 2.09 (heptet, J = 7.0 Hz, 1 H), 3.46−3.71, 3.90−4.50, 4.56−4.69 (3 m, total 4 H), 6.76, 6.83 (2 s, each 0.5 H), 6.85, 7.11 (2 br s, each 0.5 H); HRMS, calcd for $C_{16}H_{29}O_4N$ (M^+) m/z 299.2094, found 299.2083.

Mixture at C-4 of 4-Isopropyl-4-methoxy-2-[(1*R*,2*S*)-1,2-dihydroxy-2-methyloctyl]-2-butene-4-lactam (54). To a cold (0 °C) stirred solution of **53** (41 mg, 0.14 mmol) in MeOH (1 mL) was added camphorsulfonic acid (5 mg, 0.02 mmol). After stirring for 30 min, the solution was quenched with saturated aqueous $NaHCO_3$ (0.1 mL), diluted with saturated brine (20 mL), and extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give **54** (40 mg, 94%) as a colorless oil: TLC, R_f 0.50 (acetone/toluene, 1:2); $[\alpha]^{27}_D$ −10.9° (c 0.76, $CHCl_3$); IR (neat) 3250, 2950, 2930, 1690, 1640, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.84−0.89 (m, 3 H), 0.96, 0.97 (2 d, J = 7.0 Hz, each 1.5 H), 0.98, 0.99 (2 d, J = 7.0 Hz, each 1.5 H), 1.24−1.55 (m, 13 H), 2.06, 2.09 (2 heptet, J = 7.0 Hz, each 0.5 H), 3.15, 3.19 (2 s, each 1.5 H), 3.55, 3.62 (2 d, J = 8.4 Hz, each 0.5 H), 4.03, 4.15 (2 s, each 0.5 H), 4.25, 4.26 (2 d, J = 8.4 Hz, each 0.5 H), 5.86 (br s, 1 H), 6.64−6.66 (m, 1H); ^{13}C NMR (100 MHz) δ 14.1, 17.08, 17.11, 17.36, 17.41, 22.6, 22.8, 23.4, 29.87, 29.93, 31.8, 35.3, 39.2, 39.3, 50.6, 50.8, 73.6, 74.4, 74.5, 94.8, 94.9, 140.4, 140.7, 145.9, 146.0, 172.6; HRMS, calcd for $C_{16}H_{28}O_3N$ ($M^+ - OCH_3$) m/z 282.2067, found 282.2062.

Mixture at C-4 of 4-Isopropyl-4-methoxy-2-[(2*S*)-2-hydroxy-2-methyloctanoyl]-2-butene-4-lactam (PI-091) (1). To a cold (0 °C) stirred solution of **54** (17 mg, 0.053 mmol) in CH_2Cl_2 (1 mL) was added Dess−Martin periodinane (17 mg, 0.04 mmol). The mixture was stirred for 3 h, and 17 mg of the periodinane was added every 20 min. The solution was quenched with 20% aqueous $Na_2S_2O_3$ (1 mL) at 0 °C, diluted with EtOAc (20 mL), and washed with 20% aqueous $Na_2S_2O_3$ (10 mL), saturated $NaHCO_3$ (10 mL), and saturated brine (10 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give **1** (13 mg, 79%) as a colorless oil: TLC, R_f 0.69 (EtOAc/hexane, 1:1); $[\alpha]^{27}_D$ −26.4° (c 0.66, $CHCl_3$); for natural **1** $[\alpha]^{29}_D$ −26.3° (c 0.83, $CHCl_3$); IR (neat) 3270−3080, 2960, 1700, 1600, 1460 cm^{-1}; ^1H NMR (270 MHz) δ 0.84−0.88 (m, 3 H), 0.97, 0.98 (2 d, J = 7.0 Hz, each 1.5 H), 1.00, 1.01 (2 d, J = 7.0 Hz, each 1.5 H), 1.22−1.38, 1.56−1.90 (m, 10 H), 1.37, 1.38 (2 s, each 1.5 H), 2.11 (heptet, J = 7.0 Hz, 1 H), 3.17, 3.18 (2 s, each 1.5 H), 5.66, 5.69 (2 s, each 0.5 H), 6.34 (br s, 1 H), 7.56, 7.57 (2 d, J = 2.2 Hz, each 0.5 H); ^{13}C NMR (67.5 MHz) δ 14.0, 17.0, 17.2, 22.5, 23.4, 29.6, 31.7, 35.3, 38.5, 38.6, 51.1, 51.2, 75.4, 76.3, 94.5, 139.5, 139.6, 158.0, 158.1, 169.8, 198.6, 198.7; HRMS, calcd for $C_{17}H_{29}O_4N$ (M^+) m/z 311.2094, found 311.2067.

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Supporting Information Available: Copies of ^1H NMR of **14**−**16**, **18**, **20**, **23**, **37**-**43**, **45**−**48**, **51**−**54**, synthetic **1**, and natural **1**, and ^{13}C NMR of **23**, **38**, **42**, **45**, **51**, **54**, synthetic **1**, and natural **1** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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